Rational Design and First-Principles Studies toward the Remote Substituent Effects on a Novel Tetracyclic Proton Sponge

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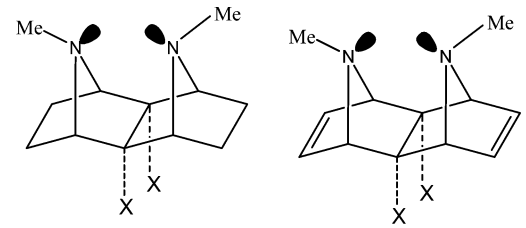
According to reliable density functional theory (DFT) calculations, 11,12-dimethyl-11,12-diazatetracyclo-[6.2.1.1^{3,6}.0^{2,7}]dodecane derivatives have been predicted as superorganic bases in the gas phase, acetonitrile, and the aqueous phase. The basicities of these tetracyclic proton sponges were modulated through remote substituent effects. Barriers for proton transfer between the N atoms of the diamine cations are also reported.

Introduction

The design and synthesis of strong organic bases has long been an active field of research.[1−6] Since the discovery of a simple organic compound 1,8-bis(dimethylamino)naphthalene (DMAN) as a superbase, which is known as a "proton sponge",[7] many proton sponges have been created and they are finding a growing number of interesting applications.[2−5] With the advent of new computer architectures and more-practical implementations of electron-correlated quantum chemical methods (such as density functional theory (DFT)), it has been feasible to apply these tools in the design of novel proton sponges or to understand the factors responsible for enhanced basicity. Quantum chemical studies have shed light on the structural factors that influence the high basicity of proton sponges.[8−12] Their abnormally high basicity is accepted to be produced by strong crowding of unshared electron pairs on N atoms, a strong intramolecular HB in the protonated form, and relief of steric strain upon protonation. However, such studies have been performed by varying the basic skeletons and the functional groups in rigid frameworks of condensed rings.[2−6] Therefore, the contributions of intramolecular HBs in the protonated form and relief of steric strain upon protonation are largely dependent on the systems used for the study. Reports on tuning proton affinities through remote substitutions, either geometrically or electronically, on same basic skeletons are not available to date.

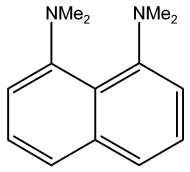
Herein, we report a novel molecular framework that differs from other proton sponges, which, however, can be remotely substituted with different functional groups to tune the geometric and electronic factors to control the basicity of these proton sponges. A tetracyclic framework (i.e., 11,12-dimethyl-11,12-diaza-tetracyclo[6.2.1.1.^{3,6}0^{2,7}]dodecane) has been substituted with *endo* and *endo*-2,7 electron donors and acceptors (see Scheme 1) to gauge the effect of such substituents on the properties of the proton sponge. The tetracyclic framework (i.e., 11,12-dimethyl-11,12-diaza-tetracyclo[6.2.1.1.^{3,6}0^{2,7}]-dodecane) ensures that the nitrogen lone pairs of electrons are present in close proximity and the rigid framework of the tetracyclic ring guarantees acid−base properties that are similar to those of the proton sponge. The geometries and proton affinities (PAs) of compounds **1**, **2**, **3**, and **4**, as well as those of DMAN (**8**) (refer to Scheme 1) were calculated using DFT.

SCHEME 1: Structures of Tetracyclic Derivatives 1−7 and DMAN (8)



1: X = H; 2: X = -CH_3
3: X = -CH_2CH_3; 4: X= -CN

5: X = H; 6: X = -CH_3
7: X= -CN



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Computational Methodology

All calculations were performed with the Jaguar program package,[13a] using Becke's three-parameter exchange functional with the correlation functional[14] of Lee, Yang, and Parr (B3LYP).[15] All species were fully optimized with a 6-31G* basis set, and harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive vibrational frequencies. Single-point calculations were then performed with the 6-311+G** basis set.[13b−d] Zero-point vibrational energies computed at the B3LYP/6-31G* level used in the PA calculations are unscaled. PAs are calculated at the B3LYP/6-311+G**//B3LYP/6-31G* level, using the general equation

$$\mathrm{PA(B)} = (\Delta E_{\mathrm{el}}) + (\Delta \mathrm{ZPVE})$$

where (ΔE_{el}) and (ΔZPVE) are the electronic and the zero-point vibrational energy contributions to the PA, respectively:

$$(\Delta E_{\mathrm{el}}) = [E(\mathrm{B}) - E(\mathrm{BH}^+)]$$

$$(\Delta \mathrm{ZPVE}) = [\mathrm{ZPVE(B)} - \mathrm{ZPVE(BH}^+)]$$

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TABLE 1: B3LYP/6-311+G//B3LYP/6-31G* Calculated Proton Affinities in the Gas Phase, Aqueous Phase (Water), and Acetonitrile**

	proton affinity, PA (kJ/mol)[a]		
compound	gas phase	aqueous phase	acetonitrile
1	1072.6	1245.0	1256.5
2	1096.1	1272.3	1273.0
3	1106.6	1282.9	1277.7
4	998.3	1200.0	1199.6
5	1062.2	1223.2	1240.8
6	1087.6	1255.0	1264.3
7	985.2	1179.0	1187.1
8	1031.0[b]	1205.3	1197.6

[a] Zero-point energy corrected. [b] Experimental value: 1030.1 kJ/mol (from ref 7).

Here, B and BH^+ denote the base in question and its conjugate acid, respectively. Molecular electrostatic potential (MESP) calculations have been performed using Jaguar with the B3LYP/6-31G* basis set.[13] The isosurface values taken for all the cases are -0.080 e/au^3. B3LYP/6-31G* optimized geometries were used to calculate the solvation energies at the B3LYP/6-311+G** level, using the Poisson−Boltzmann continuum (PB) solvent model,[16,17] as implemented in the Jaguar program.[13] In PB-based calculations of the solvation energies, the dielectric interface between the solvent and the solute is assumed to be the molecular surface, which is the contact surface between the van der Waals envelope of the solute and a probe solvent molecule (for aqueous solutions, the probe radius is 1.4 Å). The internal dielectric constant in the PB calculations is set equal to unity, because molecular polarizability is treated explicitly with quantum chemical calculations. All regions outside of the molecular surface are assigned the experimental solvent dielectric ($\epsilon = 78.4$ for aqueous solutions).

Results and Discussion

According to our DFT calculations, the parent tetracyclic compound **1** and its *endo*-substituted electron donor groups **2** and **3** have shown gas-phase proton affinities that exceed that of the proton sponge DMAN, and, in particular, the calculated PA for **3** is 81 kJ/mol higher than that for **8** (see Table 1). Interestingly, the enhancement in PA values was clearly observed for the *endo*-substituted electron donors **2** and **3**, compared to the unsubstituted derivative **1** in acetonitrile and in the aqueous phase as well (see Table 1). However, the electron-withdrawing cyano-substituted tetracyclic compound **4** has been predicted to be a poor proton sponge (see Scheme 1 and Table 1). Generally, the gas-phase PA values for **1**−**3** were observed to exceed or equal some of the higher PA values reported for aliphatic proton sponges.[10h,10i,18] Some of the principal geometrical parameters of the neutral and protonated optimized structures **1**−**4** are given in Table 2. The calculated N···N distances are ∼2.85−2.65 Å, in general agreement with the experimental values obtained for 20 proton sponges.[6] The N···N^+ distance decreases upon protonation for **1**−**4**. The computed results suggest that **1**−**4** have asymmetrical HBs in the protonated forms, with one N···H distance shorter than the other N···H distance (see Table 2). The N−H···N HB angles are in the range of 140°−145°. It is interesting to note that the N···N distance decreases with remote substitutents (see Table 2). The N···N distances are significantly shorter for **2**, **3**, and **4** than for the unsubstituted tetracyclic derivative **1**. Furthermore, the low-energy proton-transfer barriers calculated for **1** and **2** at the B3LYP/6-311+G** level (4.9 and 3.6 kJ/mol, respectively) is particularly relevant to the models of low-barrier HBs, whose role in enzyme catalysis has been debated.

TABLE 2: Calculated Geometric Parameters of Free Bases and Their Conjugate Acids at the B3LYP/6-31G* Level

	bond length (Å)			bond angle (deg)
sponge	r(N···N)	r(N···H)$^+$	r(N···H)	(N−H···N)
1	2.853			
1H$^+$	2.658	1.067	1.740	140.8
2	2.652			
2H$^+$	2.541	1.089	1.573	144.6
3	2.651			
3H$^+$	2.540	1.089	1.573	144.6
4	2.745			
4H$^+$	2.610	1.074	1.678	142.0
5	2.827			
5H$^+$	2.641	1.073	1.710	142.3
6	2.685			
6H$^+$	2.565	1.086	1.601	144.8
7	2.758			
7H$^+$	2.618	1.075	1.671	142.9
8	2.836			
8H$^+$	2.640	1.110	1.590	157.5

The unsaturated analogues **5**−**7** of 11,12-dimethyl-11,12-diaza-tetracyclo[6.2.1.1.^{3,6}0^{2,7}]dodecane derivatives were also investigated, to examine whether the further rigidity in norbornane rings enhances or reduces the PAs for the corresponding derivatives. The computed PAs for **5**−**7** are given in Table 1. The **5**−**7** tetracyclic derivatives are slightly weaker proton sponges, compared to the corresponding tetracyclic derivatives **1**−**4**. However, the relative trends of remote substituent effects toward the PA values for **5**−**7** remain similar to that of **1**−**4**. The remotely substituted electron-donating methyl group **6** enhances the PA, compared to **5**, whereas the cyano-substituted derivative **7** has significantly reduced basicity (see Table 1). The structural features for **5**−**7** also follow trends similar to those obtained for **1**−**4** (see Table 2).

The enhanced PA for **2**, **3**, and **6**, compared to their corresponding parent derivatives **1** and **5** is presumably due to the buttressing effect.[19] The remote substituents influence the −NMe groups to be closer to each other, which increases the lone-pair repulsions and, thus, destabilizes the base. As a consequence, the transition to cation provides an additional profit in energy. The calculated PAs and structural parameters (the N···N distance) support that the buttressing effect is more effective for the bulkier substituents, such as methyl and ethyl groups **2**, **3**, and **6** (see Tables 1 and 2). However, the increase in crowding of unshared electron pairs on N atoms in unprotonated forms **4** and **7**, compared to **1** and **5**, does not help to enhance the basicity in these cases. Howard concluded that the fluctutation in the basicity in the proton sponges is associated with the difference in the strength of intramolecular HBs in their cations and suggested an independent model approach to obtain the intramolecular HB energy in the protonated forms.[10] This model system represents the "atomic" framework of optimized cations. We have considered this model study to estimate the hydrogen-bond energy of **2H**$^+$, because the PA is greater than that for DMAN (**8**) (see Table 1). The HB stabilization energy can be obtained by single-point calculations (vibrationless) performed at the B3LYP/6-31G* level on the model system and their respective components at infinite separation (see Figure 1).

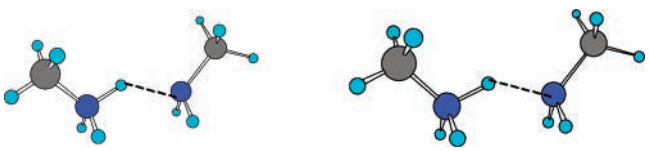

Figure 1. Model system used to estimate the hydrogen bond energy in the cation of **2H**$^+$ and **4H**$^+$.

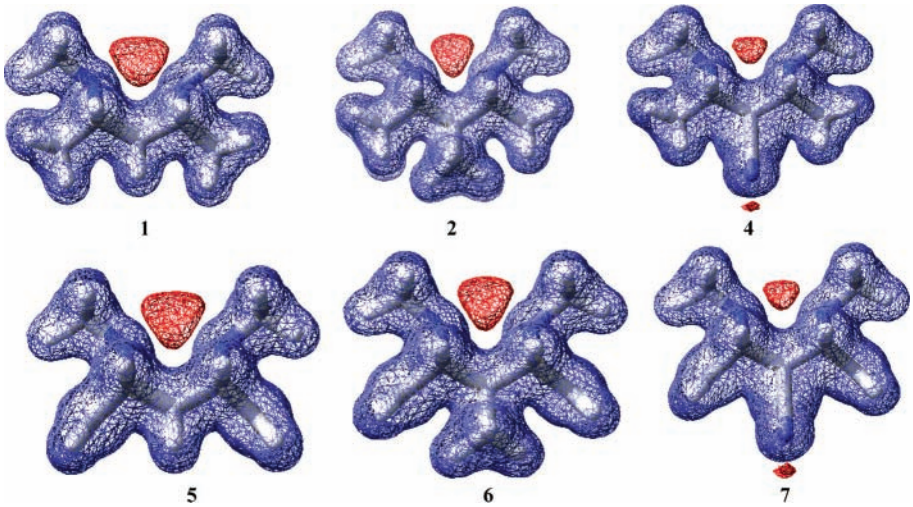

Figure 2. Molecular electrostatic isopotential surfaces of compounds **1**, **2**, **4**, **5**, **6**, and **7**.

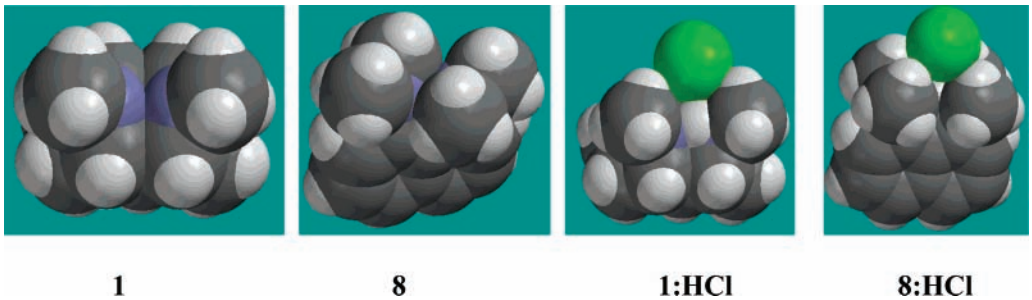

Figure 3. Structures of **1** and **8** and their HCl complexes at the B3LYP/6-31G* level. (Legend: blue = nitrogen; green = chlorine; gray = carbon; white = hydrogen.)

The estimated HB energy obtained from the model system for the protonated form of $\mathbf{2H}^+$ is 68.8 kJ/mol.[20] The HB strengths calculated for the proton sponges in earlier studies showed the energy values (~70−90 kJ/mol), where the N−H−N bond angles varied over a range of 150°−180°.[10] The linearity of HB bonds could lead to larger HB energies,[21] which was also observed for some of the known proton sponges.[10] The computed HB energy for **8** with B3LYP/6-31G* is 70.0 kJ/mol, which is slightly higher than the HB energy for $\mathbf{2H}^+$. It seems that the major difference in the basicity for **2** and **8** results from the steric strain in the unprotonated forms.[3,8,10f] The calculated steric strain in DMAN (**8**) is ~26 kJ/mol at the B3LYP level,[10] whereas the strain calculated for **2** with B3LYP6-31G* is 2.5 kJ/mol (see the Supporting Information). However, such factors are not responsible for the lower PA values of **4** and **7**. The estimated HB energy for model $\mathbf{4H}^+$ is 67.5 kJ/mol (see Figure 1), and the corresponding unprotonated form **4** is marginally strained by 2.0 kJ/mol (see the Supporting Information). Thus, the difference in the PAs for $\mathbf{2H}^+$ and $\mathbf{4H}^+$ expectedly results from the remote substituted electronic effects.

The molecular electrostatic isopotential surfaces of **1**, **2**, and **4**, and for **5**, **6**, and **7**, are shown in Figure 2. The protonation sites are more compact (shown in red in Figure 2) in the case of electron-donating methyl groups **2** and **6**. This type of region has been described previously as a hydrophobic environment at the N atoms, to which the sponge effect is attributed.[5,18] However, in the case of electron-withdrawing cyano-substituted derivatives **4** and **7**, they have, relatively, much smaller potentials (shown in red in Figure 2) close to the amino N atoms, which are seemingly responsible for the weakening the $[N-H\cdot\cdot\cdot N]^+$ HB strengths.

The discussion thus far has been concentrated on the thermodynamics of the protonation of 11,12-dimethyl-11,12-diaza-tetracyclo[6.2.1.1.^{3,6}0^{2,7}]dodecane derivatives. If these compounds can be prepared, they could prove to be practical bases, as long as they are kinetically active. Based on the examination of models and some calculations, it seems likely that this will be the case. Figure 3 shows space-filling models of **1,** DMAN (**8**), and their complexes with an external acid (HCl). DMAN (**8**) has been used as a reference, because it worked as a strong base in many experimental studies.[5,22] The minimized complexes with B3LYP/6-31G* in the gas phase (both **1** and **8**) are contact ion pairs with N−H distances of 1.058 and 1.080 Å, respectively, and H···Cl distances of 2.64 and 2.78 Å, respectively. Restricting the transfer of protons during the minimization of structures failed in each case. Therefore, it seems unlikely that proton transfer from external acids into such diamines will be prohibitive in these cases.

Conclusions

In the present study, we have shown that this novel molecular frame work can be used as superorganic bases with simple amino ($-NMe_2$) groups and by modulating the basicities from remote substituent effects. Furthermore, we have demonstrated that the remote substituents control the basicities of 11,12-dimethyl-11,12-diaza-tetracyclo[6.2.1.1.^{3,6}0^{2,7}]dodecane derivatives through geometric and electronic effects. The intramolecular proton-transfer barriers have been predicted to be lower for the compound **1** and **2** protonated systems studied here, which is particularly relevant to the models of low-barrier hydrogen bonds in enzymes. Importantly, strategies are available for the synthesis of dodecane derivatives, and, therefore, the feasibility of preparing these compounds are not a challenging task.[23] This information will stimulate the chemists to synthesize and examine the basicity of such proton sponges.

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Supporting Information Available: B3LYP/6-311+G** SCF energies, B3LYP/6-31G* zero point vibrational energies (ZPVE), and Cartesian coordinates for **1**−**7** and their monoprotonated ions. This material is available free of charge via the Internet at http://www.pub.acs.org.

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(20) To mention that the [N−H$^+$···N] bond angles in **2H**$^+$ and **4H**$^+$ are relatively smaller than the bond angle of 180° for an ideal hydrogen bond (HB). Thus, we have estimated the HB energy for 180° [N−H$^+$···N] bond angle with [$(CH_3)_3$N···H$^+$···N$(CH_3)_3$] species. The calculated HB strength is 95.0 kJ/mol for the [$(CH_3)_3$N···H$^+$···N$(CH_3)_3$] species at the B3LYP/6−31G* level and is larger than the HB energies calculated results for **2H**$^+$ and **4H**$^+$.

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